IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

ARIA DIAGNOSTICS, INC.,

Plaintiff,

v.

SEQUENOM, INC.,

Defendant/Counterclaimant.
/

No. C 11-06391 SI

CLAIM CONSTRUCTION ORDER

NATERA, INC. and DNA DIAGNOSTICS CENTER, INC.,

Plaintiffs/Counterclaim-Defendants,

v.

SEQUENOM, INC. and ISIS INNOVATION LIMITED,

Defendants/Counterclaimants.
/

No. C 12-00132 SI

VERINATA HEALTH, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

SEQUENOM, INC. and SEQUENOM CENTER FOR MOLECULAR MEDICINE, LLC,

Defendants/Counterclaimants.
/

No. C 12-00865 SI

VERINATA HEALTH, INC. and THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY,

Plaintiffs,

v.

ARIOSA DIAGNOSTICS, INC. and LABORATORY CORPORATION OF AMERICA HOLDINGS,

Defendants/Counterclaimants.
/

No. C 12-05501 SI

On September 12, 2013 and September 16, 2013, the Court held *Markman* hearings regarding the construction of disputed claim terms in six patents teaching techniques for non-invasive prenatal testing. Having considered the arguments of counsel and the papers submitted, the Court construes the disputed claim terms as follows.

BACKGROUND

1. Procedural Background

This dispute began in 2011, when Ariosa[1] filed a declaratory relief action against Sequenom, seeking a declaration that its "Harmony Test" does not infringe any claims of U.S. Patent No. 6,258,540 ("the '540 patent"). *Aria Diagnostics, Inc. v. Sequenom, Inc.*, C 11-6391-SI (filed Dec. 19, 2011). Sequenom filed a counterclaim against Ariosa, asserting infringement of the '540 patent. Subsequently, two other companies, Natera and Verinata, also filed declaratory judgment actions in this Court seeking judgments that their products do not infringe Sequenom's '540 patent and asserting that the '540 patent is invalid. *See Natera Inc. v. Sequenom, Inc.*, C 12-0132-SI (filed Jan. 6, 2012) (regarding the "Non-Invasive Paternity Test"); *Verinata Health, Inc. v. Sequenom, Inc. (Verinata I)*, C 12-0865-SI (filed Feb. 22, 2012) (regarding the "Verifi Prenatal Test"). Sequenom also filed counterclaims that Natera, DNA Diagnostics Center, Verinata, and Stanford are infringing the '540 patent. *See id.*

Additionally, in *Verinata I*, Verinata and Stanford allege that Sequenom is infringing U.S. Patent Nos. 7,888,017 ("the '017 patent"), 8,008,018 ("the '018 patent"), and 8,195,415 ("the '415 patent"). Finally, Verinata and Stanford also filed a case alleging that Ariosa and LabCorp are infringing U.S. Patent Nos. 8,296,076 ("the '076 patent") and 8,318,430 ("the '430 patent"). *See Verinata Health, Inc. v. Ariosa Diagnostics, Inc. (Verinata II)*, C 12-5501-SI (filed Oct. 25, 2012).

2. Factual Background

These patents all involve methods to conduct non-invasive prenatal DNA testing. Fetal DNA

[1] Formerly known as Aria Diagnostics, Inc.

testing can aid sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother. It can also detect fetal aneuploidy, which is a disorder in which the fetus has an abnormal number of chromosomes, instead of the normal 23 pairs. Common aneuploidy disorders include Down syndrome (a third copy, or "trisomy," of chromosome 21), Edwards syndrome (a third copy of chromosome 18), and Patau syndrome (a third copy of chromosome 13).

Prior to these patents, testing fetal DNA required invasive techniques that took samples from the fetus or placenta. However, invasive prenatal testing presented risks to both the fetus and the mother. Scientists began researching various techniques to make these prenatal diagnoses non-invasively. Initially, non-invasive research had focused on detecting fetal cells that had passed through the amniotic sac into the mother's bloodstream. The fetal cells then had to be separated from the much more common maternal cells. This process of isolating intact fetal cells was labor-intensive and produced unreliable results.

The '540 patent followed the discovery in 1996-1997 by Drs. Lo and Wainscoat that fetal DNA is detectable in maternal serum or plasma samples in extra-cellular or cell-free form. According to Sequenom, prior non-invasive research had focused on detecting fetal cells because the presence of cell-free fetal DNA was not known. Evans Decl. ¶ 40. Therefore, the significance of the discovery by Drs. Lo and Wainscoat was that the process of isolating fetal cells was not necessary because fetal DNA was present outside of cells, as "extracellular" or "cell-free DNA" suspended together with the mother's DNA in the maternal bloodstream. This was a more efficient and reliable method then previous non-invasive techniques.

A decade later, Drs. Quake and Fan at Stanford further advanced the science in non-invasive prenatal testing using molecular counting techniques. Previously, researchers had believed that because aneuploidies do not present a mutational change in the DNA sequence (but are merely a change in the number of chromosomes), they would need to distinguish fetal DNA from maternal DNA in order to diagnose fetal aneuploidy non-invasively. The Stanford researchers used advanced DNA sequencing techniques, such as digital polymerase chain reaction ("PCR") and massive parallel sequencing. They discovered a method to diagnose fetal aneuploidy through their molecular counting techniques, without needing to distinguish the maternal DNA from the fetal DNA. Stanford and Verinata claim that these

techniques are much more efficient and effective than those utilized previously. They further refined their method by teaching how to correct for sequence tag density variances, how to selectively analyze specific DNA sequences, and how to generate a library from a pool of multiple samples. These advancements further increased the accuracy and the efficiency of the prenatal tests.

LEGAL STANDARD

Claim construction is a matter of law. *Markman v. Westview Instr., Inc.*, 517 U.S. 370, 372 (1996). Terms contained in claims are "generally given their ordinary and customary meaning." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Id.* at 1312. In determining the proper construction of a claim, a court begins with the intrinsic evidence of record, consisting of the claim language, the patent specification, and, if in evidence, the prosecution history. *Id.* at 1313; *see also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "The appropriate starting point . . . is always with the language of the asserted claim itself." *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186 (Fed. Cir. 1998); *see also Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997).

Accordingly, although claims speak to those skilled in the art, claim terms are construed in light of their ordinary and accustomed meaning, unless examination of the specification, prosecution history, and other claims indicates that the inventor intended otherwise. *See Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1053 (Fed. Cir. 1994). The written description can provide guidance as to the meaning of the claims, thereby dictating the manner in which the claims are to be construed, even if the guidance is not provided in explicit definitional format. *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1344 (Fed. Cir. 2001). In other words, the specification may define claim terms "by implication" such that the meaning may be "found in or ascertained by a reading of the patent documents." *Vitronics*, 90 F.3d at 1584 n.6.

In addition, the claims must be read in view of the specification. *Markman*, 52 F.3d at 978. Although claims are interpreted in light of the specification, this "does not mean that everything

expressed in the specification must be read into all the claims." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957 (Fed. Cir. 1983). For instance, limitations from a preferred embodiment described in the specification generally should not be read into the claim language. *See Comark*, 156 F.3d at 1187. However, it is a fundamental rule that "claims must be construed so as to be consistent with the specification." *Phillips*, 415 F.3d at 1316. Therefore, if the specification reveals an intentional disclaimer or disavowal of claim scope, the claims must be read consistently with that limitation. *Id.*

Finally, the Court may consider the prosecution history of the patent, if in evidence. *Markman*, 52 F.3d at 980. The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution. *See Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). In most situations, analysis of this intrinsic evidence alone will resolve claim construction disputes. *See Vitronics*, 90 F.3d at 1583. Courts should not rely on extrinsic evidence in claim construction to contradict the meaning of claims discernable from examination of the claims, the written description, and the prosecution history. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583). However, it is entirely appropriate "for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field." *Id.* Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317. All extrinsic evidence should be evaluated in light of the intrinsic evidence. *Id.* at 1319.

DISCUSSION

1. Sequenom's '540 Patent

Sequenom is the exclusive licensee of the '540 patent, which Sequenom licensed from Isis Innovation Limited. The '540 patent is entitled "Non-Invasive Prenatal Diagnosis," and was issued to Drs. Yuk-Ming Dennis Lo and James Stephen Wainscoat on July 10, 2001. The patent "relates to a detection method performed on a maternal serum or plasma sample from a pregnant female, which method comprises detecting the presence of a nucleic acid of foetal origin in the sample." The '540

Patent, Abstract. "This invention enables non-invasive prenatal diagnosis, including for example sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother." *Id*.

The '540 Patent application was originally filed in 1998, and underwent two rounds of rejections before the patent issued in 2001. In that process, the PTO required the applicants to include the limitation "paternally inherited" in claims where the applicants had wanted to use simply "nucleic acid" or "foetal nucleic acid." The PTO also required the applicants to add "amplifying."

Relevant for the purposes of this motion, the '540 patent claims the following:

> **Claim 1.** A method for **detecting a paternally inherited nucleic acid of fetal origin** performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> **amplifying a paternally inherited nucleic acid** from the serum or plasma sample and
>
> **detecting the presence of a paternally inherited nucleic acid of fetal origin** in the sample.
>
> **Claim 8.** The method according to claim 1, wherein the presence of a foetal nucleic acid from a **paternally-inherited non-Y chromosome** is detected.
>
> **Claim 13.** The method according to claim 5, which comprises **determining the concentration** of the foetal nucleic acid sequence in the maternal serum or plasma.
>
> **Claim 19.** The method according to claim 1, wherein the sample contains foetal DNA at a fractional concentration of total DNA of at least about 0.14%, without subjecting it to a **foetal DNA enrichment step**.

The '540 Patent 23:60-67, 25:39-42 (the construction of the highlighted terms is disputed by the parties). Most of the claims are dependent on claim 1. The parties agree that terms should be construed consistently across all claims, and that "according to the method of claim 1" from claim 21 means "claim 21 is dependent on claim 1 and therefore incorporates all the limitations of claim 1."

On July 5, 2012, the Court denied Sequenom's motion for a preliminary injunction, in the course of which it preliminarily construed two terms from the '540 patent, "paternally inherited nucleic acid" and "amplifying." Sequenom appealed the Court's order. On August 9, 2013, the Federal Circuit issued an order rejecting the Court's initial claim construction. *Aria Diagnostics, Inc. v. Sequenom, Inc.*, No. 2012-1531, 2013 WL 4034379 (Fed. Cir. Aug. 9, 2013). The Federal Circuit found that "paternally inherited nucleic acid" did not need to be known in advance to have been inherited only from the father. *Id.* at *2-5. The Federal Circuit also found the term "amplifying" was not limited to increasing the

concentration, but more broadly means increasing the amount. *Id.* at *5-6. The Court construes these terms and other disputed terms in the '540 patent in accordance with the Federal Circuit order.

"Paternally inherited nucleic acid," therefore, is construed as "a nucleic acid that originates from the fetus and is inherited from the father."[2] **"Amplifying,"** therefore, is construed as "increasing the amount of the nucleic acid by making copies of it."

The parties dispute the construction of four other terms.

A. "Detecting"

Claim Term	Sequenom's Proposed Construction	Ariosa's Proposed Construction	Natera/DDC's Proposed Construction	Verinata's Proposed Construction
"detecting" / "detecting a paternally inherited nucleic acid" / "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample" / "to detect paternally inherited nucleic acid" / "subjecting the amplified nucleic acid to a test for the paternally inherited nucleic acid" [Claims 1, 4, 5, 8, 15, 18, 21, 24, 25]	Construe "detecting" as: "discovering or determining the existence, presence, or fact of" See above for "paternally inherited nucleic acid." "Subjecting" and "test" have their ordinary and customary meanings	"discovering (the presence of) a DNA sequence known to be received only from the father which is not possessed by the mother; the discovering is not based on differences between maternal and fetal DNA"	"discovering (the presence of) a fetal DNA sequence from a primer binding region inherited from the father and previously known to not be possessed by the mother; the discovering is not based on differences between maternal and fetal DNA"	"isolating and identifying any paternal nucleic acid by comparison to maternal characteristics"

[2] Subsequent to the Federal Circuit's opinion, the parties revised several of their proposed constructions. Natera currently proposes that this term be construed as "a fetal DNA sequence from a primer binding region inherited from the father and previously known to not be possessed by the mother." However, the Court finds that it is bound by the findings of the Federal Circuit, which require these constructions. Natera's modified proposal is not consistent with the Federal Circuit opinion.

Sequenom, Ariosa, and Natera essentially agree that detecting means discovering, but disagree about whether the detecting can be based on differences between maternal and fetal DNA. Verinata's amended proposed construction is based on language from the Federal Circuit's order.

Ariosa and Natera argue that the limitation "the discovering is not based on differences between maternal and fetal DNA" is required to ensure that the claims are limited to the detection of fetal nucleic acid *known* to be received from the father and not possessed by the mother. They also variously add the phrases "known to be received only from the father" or "previously known to not be possessed by the mother" to accomplish this same purpose. They cite to the prosecution history and specification as support for their proposed constructions. This is essentially the same argument that the parties made in their proposed construction for "paternally inherited nucleic acid."

The Federal Circuit has rejected an interpretation of the prosecution history requiring that the paternal origin be known in advance, finding the prosecution events "ambiguous." *Aria Diagnostics*, 2013 WL 4034379, at *4 ("This [prosecution history] record does not clearly require that the paternally inherited sequence must have been known in advance to have come from the father. The account of the prosecution history makes no reference to advance timing, let alone the clear and unmistakable disavowal required by controlling precedent."). The Federal Circuit also rejected the argument that this known in advance limitation was required by the specification or the examples. *Id.* at 3-4.

Thus, the parties cannot add the same "known in advance" limitation to the "detecting" term. It is not supported by the plain language of the term. There is not a clear limitation that the paternal inheritance must be known in advance or that the detecting cannot be not based on differences between maternal and fetal DNA.

Verinata's proposed construction is taken from the following portion of the Federal Circuit opinion: "Properly understood, this sentence describes the method of isolating and identifying *any* paternal characteristics by comparison to maternal characteristics, hardly a limitation to *only* paternal characteristics known in advance." *Id.* at *4 (emphasis in original). However, this passage explains the meaning of a sentence in the specification; it does not construe the "detecting" term or any other claim term. Moreover, this proposed construction is not supported by the claim or specification. The word "identifying" is never used in the patent, and nothing in the specification requires limiting the scope of

detecting is limited only to "comparison to maternal characteristics." Even if all of the examples detect through a comparison to maternal characteristics, the Federal Circuit opinion is clear that these examples do not limit the claim scope. *See id.* at *3 ("Instead of a clear intention to limit the claims to the embodiments in the examples, here the specification states that the examples 'do not in any way limit the scope of the invention.'").

"**Detecting,"** therefore is construed as "discovering or determining the existence, presence, or fact of."

B. "Foetal DNA Enrichment Step"

Claim Term	Sequenom's Proposed Construction	Ariosa's Proposed Construction	Natera/DDC's Proposed Construction	Verinata's Proposed Construction
"foetal DNA enrichment step" [Claim 19]	"increasing the concentration of fetal DNA relative to the maternal DNA in the sample"	See below	Because claim 19 is not asserted in this case, it is not appropriate to construe this term.	See below
"without subjecting it to a foetal DNA enrichment step" [Claim 19]	See above	"prior to the amplification step of claim 1"		"prior to the amplification step of claim 1"

The parties' dispute regarding the term "foetal DNA enrichment step" is essentially a continuation of the argument previously made about "amplifying." Sequenom argues that enrichment is a distinct term, and should be construed differently from amplification. Ariosa and Verinata argue that the enrichment term is equivalent to "amplifying" in claim 1, and therefore "without subjecting it to a foetal DNA enrichment step" should be construed as "prior to the amplification step of claim 1." Natera contends that because claim 19 is not asserted in this case, it is not appropriate to construe this term.

The Federal Circuit rejected the argument that amplifying means increasing the concentration, and found that "the specification discloses that 'enrichment' and 'amplification' are distinct." *Aria*

Diagnostics, 2013 WL 4034379, at *5. It also found that the prosecution history was insufficient to constitute a clear disavowal of the broad language of the claim. *Id.* at *6. Therefore, the "enrichment step" must not refer to the amplification step of claim 1, but instead describes an action, enrichment, which has a distinct meaning from amplification.

The Court disagrees with Natera, and finds that this claim should be construed because it is being asserted against at least one of the parties.

"**Foetal DNA enrichment step**" is construed as "increasing the concentration of fetal DNA relative to the maternal DNA in the sample."

C. "Fetal/foetal"

Claim Term	Sequenom's Proposed Construction	Ariosa's Proposed Construction	Natera/DDC's Proposed Construction	Verinata's Proposed Construction
"fetal" / "foetal"	No construction needed – ordinary and customary meaning: "of or from a fetus"	"of pregnancies from 7 to 40 weeks of gestation"		

Ariosa contends that "fetal" should be construed as "of pregnancies from 7 to 40 weeks of gestation" because the specification states that "[s]ex determination has successfully been performed on pregnancies from 7 to 40 weeks of gestation."

However, this statement in the specification does not rise to the level of clear disavowal of scope limiting "fetus" to 7 to 40 weeks of gestation, or a clear lexicography of the term. The statement merely remarks on the window for successful sex determination; it says nothing about the definition of a fetus or the possibilities of doing other prenatal tests within this time frame. Morever, this term has an ordinary and plain meaning that is known to both persons having ordinary skill in the art and lay persons. "The ordinary meaning of claim language may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1360 (Fed. Cir. 2008) (quotations omitted).

Therefore, the Court finds that this term does not require construction.

D. "Determining the Concentration"

Claim Term	Sequenom's Proposed Construction	Ariosa's Proposed Construction	Natera/DDC's Proposed Construction	Verinata's Proposed Construction
"determining the concentration" [Claim 13]	No construction needed – ordinary and customary meaning: "determining the concentration of foetal nucleic acid in the maternal sample"	Ariosa does not propose a construction, as Sequenom has not asserted claim 13 against Ariosa. Ariosa reserves its rights with respect to this term.	Indefinite	

In the joint claim construction brief Natera argues that this term is indefinite, but in its moving papers it makes no argument regarding this term. The Court finds that the term is not indefinite, but has an ordinary and customary meaning and no construction is needed.

2. The '017 and '018 Patents (Verinata and Stanford)

On February 15, 2011, the PTO issued the '017 patent, entitled "Non-invasive Fetal Genetic Screening by Digital Analysis," and on August 30, 2011, it issued the '018 patent, entitled "Determination of Fetal Aneuploidies by Massively Parallel DNA Sequencing." The '018 patent is a continuation of the '017 patent, and has a nearly identical specification. Stanford is the patent owner and Verinata is the exclusive licensee of these patents. They allege that Sequenom is infringing these patents. *See Verinata I.*

The patents explain that "[s]ince aneuploidies do not present a mutational change in sequence, and are merely a change in the number of chromosomes, it has not been possible to detect them in a fetus without resorting to invasive techniques," because researchers believed that determining whether a fetus was carrying an extra chromosome required distinguishing fetal DNA from maternal DNA. The '017 Patent, Abstract. However, the patent inventors discovered that "digital amplification allows the detection of aneuploidy using massively parallel amplification and detection methods." *Id.* By using

sophisticated molecular counting techniques, the researchers could determine small under- or over-representations of a chromosome that would reveal fetal aneuploidy, without the need to distinguish between the maternal and fetal DNA. *See id.* 21:10-30.

The relevant portion of the '017 patent claims the following:

> **Claim 17.** A method for determination of the presence or absence of a fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA, wherein the method comprises:
>
> a) obtaining a mixture of fetal and maternal genomic DNA from said maternal tissue sample;
>
> b) distributing random fragments from the mixture of fetal and maternal genomic DNA of step a to provide **reaction samples containing a single genomic DNA molecule or amplification products of a single genomic DNA molecule**;
>
> c) conducting **massively parallel DNA sequencing of the random fragments of genomic DNA** in the reaction samples of step b) to determine the sequence of said random fragments;
>
> d) **identifying the chromosomes** to which the sequences obtained in step c) belong;
>
> e) **analyzing the data of step d) to determine I) the number of copies of at least one first target chromosome in said mixture of fetal and maternal genomic DNA, wherein said at least one first target chromosome is presumed to be diploid** in both the mother and the fetus, **and ii) the number of copies of a second target chromosome** in said mixture of fetal and maternal genomic DNA, **wherein said second chromosome is suspected to be aneuploid** in the fetus;
>
> f) conducting **a statistical analysis that compares the number of copies of said at least one first target chromosome to the number of copies of said second target chromosome**; and
>
> g) **determining the presence or absence of a fetal aneuploidy from the results of the statistical analysis of step f).**

The '017 Patent 35:11-25 (the construction of the highlighted terms is disputed by the parties). Also relevant, the '018 patent claims the following:

> **Claim 1.** A method for determining presence or absence of fetal aneuploidy in a maternal tissue sample comprising fetal and maternal genomic DNA, wherein the method comprises:
>
> a. obtaining a mixture of fetal and maternal genomic DNA from said maternal tissue sample;
>
> b. conducting **massively parallel DNA sequencing of DNA fragments randomly selected** from the mixture of fetal and maternal genomic DNA of step a) to determine the sequence of said DNA fragments;
>
> c. **identifying chromosomes** to which the sequences obtained in step b) belong;

> d. using the data of step c) to **compare an amount of at least one first chromosome in said mixture of maternal and fetal genomic DNA to an amount of at least one second chromosome in said mixture** of maternal and fetal genomic DNA, **wherein said at least one first chromosome is presumed to be euploid** in the fetus, **wherein said at least one second chromosome is suspected to be aneuploid** in the fetus, thereby determining the presence or absence of said fetal aneuploidy.
>
> **Claim 3.** The method of claim 1 wherein said massively parallel DNA sequencing comprises I) attaching said DNA fragments to a planar optically transparent surface; ii) conducting **solid phase amplification of the attached DNA fragments to create a high density sequencing flow cell**, and iii) sequencing of the amplified DNA fragments in the high density sequencing flow cell by a **four-color DNA sequencing by synthesis process**.

The '018 Patent 33:58-62, 34:49-57 (the construction of the highlighted terms is disputed by the parties). The parties agree that the terms "aneuploidy" in both the '017 and the '018 patent should be construed as "the occurrence of one or more extra or missing chromosomes." They dispute the construction of the following terms in the '017 and '018 patents.

A. "Massively Parallel DNA Sequencing"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"massively parallel DNA sequencing" [Claim 17 of the '017 patent]	"any sequencing method that allows for the acquisition of sequence information from multiple DNA fragments in parallel (*e.g.*, the Illumina sequencing platform)"	See below
"massively parallel DNA sequencing of the random fragments of genomic DNA" [Claim 17 of the '017 patent]	See above	"massively parallel DNA sequencing of the random fragments of genomic DNA in each discrete reaction sample to detect the presence of the target sequence"
"massively parallel DNA sequencing" [Claim 1 of the '018 patent]	"any sequencing method that allows for the acquisition of sequence information from multiple DNA fragments in parallel (*e.g.*, the Illumina sequencing platform)"	See below
"massively parallel DNA sequencing of DNA fragments randomly selected" [Claim 1 of the '018 patent]	See above	"random, not targeted, massively parallel DNA sequencing"

Sequenom argues that the differences between "random fragments of genomic DNA" from the '017 patent and "DNA fragments randomly selected" from the '018 patent mean that the sequencing in the '017 patent is targeted, while the sequencing in the '018 patent is not targeted but random. Verinata argues that "massively parallel DNA sequencing" in the '017 and '018 patents should be construed identically, and neither term is limited to targeted DNA sequencing.

The Federal Circuit has held that in patents derived from the same application, claims should be interpreted consistently across all patents, and courts should "draw distinctions between the various patents only where necessary." *NTP, Inc. v. Research In Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005). Here, where the '017 and the '018 patents share an identical specification, these terms should be construed identically, unless the Court finds it necessary to draw a distinction.

The claim language supports the interpretation that both patents encompass random DNA sequencing. The sequencing is performed on "random fragments" or "DNA randomly selected." Additionally, the sequencing step in both patents is followed by the identical step of "identifying the chromosomes to which the sequences obtained in [the sequencing step] belong." The '017 Patent 35:26-27; The '018 Patent 33:57-58. Thus, it is clear from the order of the steps that first the "random" DNA fragments undergo sequencing, and then the sequences are identified. If the sequencing was targeted, then the identity of the targeted sequences would already be known. This would render the identification step in the '017 patent superfluous, which is insupportable. *See Aristocrat Technologies Australia Pty Ltd. v. Int'l Game Tech.*, 709 F.3d 1348, 1358 (Fed. Cir. 2013).

Sequenom argues that the identification step would not be superfluous, because it would be necessary to determine whether the sequences are from the first or second target chromosome. However, this is not supported by the specification, which explains that detection may be carried out by "directly sequencing a region of interest to determine if it is the target sequence of interest," not whether it is one of the target sequences. The '017 Patent 12:32-33. Thus, the specification and the claim language support an identical construction encompassing random sequencing.

Sequenom also argues that the prosecution history supports its proposed construction. It argues that during the prosecution of Dr. Quake's '833 continuation application, the PTO determined that the specification does not support random sequencing, and is limited to targeted sequencing. The PTO

stated that it did not find Stanford's arguments compelling "because the term 'random sequencing' appears to be a term of art, which is distinguishable from a process of just sequencing an unknown sequence," and the PTO examiner found that the patent "does not appear to support the claimed limitation directed to 'randomly sequencing.'" Holmes Decl., Ex. 40 at 2, 4. However, the applicants repeatedly rebutted the examiner, instead of disavowing the claim scope. An "examiner's unilateral remarks [do] not alter the scope of the claim. An examiner's statement cannot amend a claim." *Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1347 (Fed. Cir. 2005). Instead of clearly disavowing the scope of the claim, the applicants presented evidence refuting the examiner's concerns.

The Court finds there was no clear disavowal of claim scope in either the prosecution history or the specification, especially in light of the Federal Circuit's instruction to construe claims from the same patent family identically unless it is necessary to do otherwise.

Additionally, the Court finds that the specification supports Verinata's proposed construction:

> A methodology useful in the present invention platform is based on *massively parallel sequencing of millions of fragments using attachment of randomly fragmented genomic DNA* to a planar, optically transparent surface and solid phase amplification to create a high density sequencing flow cell with millions of clusters, each containing ~1,000 copies of template per sq. em. These templates are sequenced using four-color DNA sequencing-by-synthesis technology. *See, products offered by Illumina, Inc*., San Diego Calif. Also, see US 2003/0022207 to *Balasubramanian*, et al., published Jan. 30, 2003, entitled "Arrayed polynucleotides and their use in genome analysis." . . . *Only about 30 bp of random sequence information are needed to identify a sequence* as belonging to a specific human chromosome.

The '017 Patent 20:1-18 (emphasis added). The specification's description of sequencing millions of fragments of randomly fragmented DNA, and then identifying the sequence as belonging to a specific human chromosome, is aligned with random, not targeted, sequencing. Moreover, Sequenom does not dispute that the Illumina platform and the Balasubramanian patent application both support random massively parallel sequencing.

Sequenom argues that Verinata's proposed construction is overbroad because it encompasses both targeted and random massively parallel sequencing, as well as first generation parallel sequencing technology, such as Sanger Sequencing, that a person having ordinary skill in the art would not consider massively parallel sequencing.

Sequenom also objects to the parenthetical example "(*e.g.*, the Illumina sequencing platform)." It argues that on the priority date, February 2006, no Illumina products existed and the specification did not describe an Illumina sequencing platform. However, the final version of the specification does include references to the Illumina sequencing platform. *Sun. Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1388 (Fed. Cir. 2010) (holding that in claim construction, "the specification to be consulted is that of the issued patent, not an earlier application"). Verinata explains that the technology was known as "Solexa" before Illumina acquired it in late 2006, and Verinata would be amenable to changing the construction to "the Solexa/Illumina sequencing platform." A person having ordinary skill in the art would understand this reference, and it has appeared in the art in this format. *See, e.g.*, Gauger Decl., Ex. 5 (A fact sheet from Sequenom referencing "Solexa/Illumina (and other next generation sequencing technologies)"). Moreover, the addition of this example resolves Sequenom's concern about the construction being too broad and including first generation parallel sequencing; the exemplar clarifies the type of sequencing for a person having ordinary skill in the art.

"Massively parallel DNA sequencing," therefore, is construed as "any sequencing method that allows for the acquisition of sequence information from multiple DNA fragments in parallel (*e.g.*, the Solexa/Illumina sequencing platform)."

B. "Reaction Samples"

Claim Term	**Verinata's Proposed Construction**	**Sequenom's Proposed Construction**
"reaction samples containing a single genomic DNA molecule or amplification products of a single genomic DNA molecule" [Claim 17 of the '017 patent]	"reaction samples containing a single DNA fragment or the amplification products of a single DNA fragment"	"discrete reaction samples where the target sequence can be analyzed and where the number of reaction samples is selected to give a statistically significant result for the number of copies of a target in the DNA molecule"

The parties' dispute regarding the construction of this term is a continuation of the previous dispute about whether the sequencing in the '017 patent is targeted or random. Sequenom's proposed construction adds a number of phrases not present in the claim or the specification, and restricts the

claim to targeted DNA sequencing. As the Court explained *supra*, it does not find that there was a clear disavowal of the claim scope in the prosecution or specification that would limit claim 17 to targeted sequencing.

Moreover, many of Sequenom's other additions are not supported by the specification. For example, the specification is not limited to a "statistically significant result." It states that the number of samples is chosen "for the results desired," and although in some tests at least 10,000 samples are preferred for "a high degree of statistical significance, "results can be obtained with less, e.g. on the order of about 500 samples." The '017 Patent 5:54-6:3. Thus, there is an embodiment for results that are not statistically significant, and nothing in the specification clearly limits the claim to statistically significant results.

Verinata's proposed construction substitutes "DNA fragment" for "genomic DNA molecule." This is supported by the claim language, because the earlier portion of step (b) refers to DNA fragments, and step (c) states that what are sequenced in the "reaction samples" are the "fragments of genomic DNA."

"**Reaction samples containing a single genomic DNA molecule or amplification products of a single genomic DNA molecule,"** therefore, is construed as "reaction samples containing a single DNA fragment or the amplification products of a single DNA fragment."

C. "Identifying [the] Chromosomes"

Claim Term	**Verinata's Proposed Construction**	**Sequenom's Proposed Construction**
"identifying the chromosomes" [Claim 17 of the '017 patent]	No construction necessary	"determining the identity of the unique regions of the target chromosome from the corresponding target sequences"
"identifying chromosomes" [Claim 1 of the '018 patent]	No construction necessary	"aligning sequences obtained from random massively parallel DNA sequencing to a reference genome"

The parties dispute the construction of these nearly identical terms in the '017 and the '018 patents. Verinata argues that no construction is necessary, and Sequenom argues that they should be construed differently, based on its argument that the '017 patent enables targeted sequencing while the '018 patent enables random sequencing.

Sequenom argues that the word "the" in the '017 patent signifies that the term is referencing target chromosomes, while the lack of "the" in the '018 patent signifies that there were no target chromosomes. However, it would be a large leap to import such a distinction from the presence or absence of the word "the." This does not comport with how a person of ordinary skill in the art would understand this term. Moreover, as discussed *supra*, the Court has rejected Sequenom's argument and found that the '017 patent is not limited to targeted sequencing. These nearly identical terms, in patents with nearly identical specifications, should be given the same meaning, unless it is "necessary" for the Court to give them a different meaning. A vastly different construction is not supported by the difference of a mere article. Sequenom has offered no support for its contention that these terms should be given different constructions.

The Court finds that these terms need no construction and should be accorded their plain and ordinary meaning. "The ordinary meaning of claim language may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *O2 Micro Int'l Ltd.*, 521 F.3d at 1360 (quotations omitted). There is nothing technical or difficult about these terms, and their meaning would be readily apparent even to lay persons.

"Identifying chromosomes" and **"identifying the chromosomes,"** therefore, shall be accorded their plain and ordinary meaning because no construction is necessary.

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D. "Analyzing the Data of Step D"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"analyzing the data of step d) to determine I) the number of copies of at least one first target chromosome in said mixture of fetal and maternal genomic DNA, wherein said at least one first target chromosome is presumed to be diploid . . . and ii) the number of copies of a second target chromosome" [Claim 17 of the '017 patent]	"determining the number of copies of at least one first target chromosome in said mixture of fetal and maternal genomic DNA . . . and ii) the number of copies of a second target chromosome, as represented by the identifying step d)"	"determining the integer number of copies of the target chromosomes in said mixture of fetal and maternal genomic DNA from the identities of the target chromosomes determined in step d)"

The essential dispute between the parties centers on how to define the "number of copies," and whether that number is necessarily an "integer" number.

Verinata argues that "integer" is not found anywhere in the patent. Verinata explains that this is because whole chromosomes are rarely found in the plasma, and the claim specifically refers to DNA "fragments," not whole integers. Sequenom cannot point to any portion of the specification that limits this step to whole integers, instead of numbers. Indeed, the specification refers to an example finding "2.03 amplicons from chromosome B." The '017 Patent 21:25-26. Although Sequenom disputes the relevance of "amplicons" to this step, there is nothing in the specification or the claim that limits this term to whole integers. Additionally, the patent also contains an example, Table 1, wherein the patent shows the results from a digital PCR analysis in a "ratio" format, not in whole integers. *Id.* at 28:5-24. Thus, there is no clear disavowal of the claim scope that would require limiting the analysis to an integer result.

"Analyzing the data of step d) to determine I) the number of copies of at least one first target chromosome in said mixture of fetal and maternal genomic DNA, wherein said at least one first target chromosome is presumed to be diploid . . . and ii) the number of copies of a second target chromosome," therefore, is construed as "determining the number of copies of at least one first target chromosome in said mixture of fetal and maternal genomic DNA . . . and ii) the number of copies of a second target chromosome, as represented by the identifying step d)."

F. "First Chromosome Presumed"; "Second Chromosome Suspected"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"wherein said at least one first target chromosome is presumed to be diploid" [Claim 17 of the '017 patent]	"wherein said first target chromosome is presumed to be of normal copy number"	"wherein an affirmative presumption is made that the at least one first target chromosome, which cannot include the at least one second chromosome suspected to be aneuploid, is of normal copy number"
"wherein said at least one second chromosome is suspected to be aneuploid" [Claim 17 of the '017 patent]	"wherein said second chromosome is suspected to be of abnormal copy number"	"wherein there is an affirmative suspicion that at least one second chromosome is of abnormal copy number"
"wherein said at least one first chromosome is presumed to be euploid" [Claim 1 of the '018 patent]	"wherein said first chromosome is presumed to be of normal copy number"	"wherein an affirmative presumption is made that at least one first chromosome, which cannot include the at least one second chromosome suspected to be aneuploid, is of normal copy number"
"wherein said at least one second chromosome is suspected to be aneuploid" [Claim 1 of the '018 patent]	"wherein said second chromosome is suspected to be of abnormal copy number"	"wherein there is an affirmative suspicion that at least one second chromosome is of abnormal copy number"

The parties agree that the proper meaning for "diploid" and "euploid" is "of normal copy number," and similarly that the proper meaning of "aneuploid" is "of abnormal copy number." The parties disagree about two other aspects of this term. First, Sequenom argues that the presumptions or suspicions in these terms must be "affirmative," while Verinata argues there is no support for this limitation. Second, Sequenom argues that the claim is limited so that the second chromosome cannot also be suspected to be aneuploid.

The Court finds that Sequenom's additional limitation of "affirmative" is not supported by the claim or specification. "Affirmative" is not even mentioned in the patents. Additionally, it may add confusion rather than clarity to the patent. The aneuploidies tested for are quite rare in the general population. It is only comparison to other chromosomes that makes certain trisomies more probable. Generally, a fetus could not survive with an aneuploidy of chromosome 1, while it might survive an

aneuploidy of chromosome 21. Thus, a person having ordinary skill in the art would understand that, in analyzing these two chromosomes, chromosome 1 would be the control chromosome because it is more likely to be euploid. However, although in comparison chromosome 21 is more likely to be aneuploid, the actual probability of chromosome 21 trisomy is quite low in the general population. Limiting the claim to an "affirmative" suspicion could add confusion or imply a limitation that is not supported by the patent. The examples in the patent do not require a special reason to suspect that the chromosome of a particular fetus is aneuploid beyond the numbers in the general population (for example because the mother is over the age of 35). Sequenom's expert confirmed this, and agreed that the claim covered "the situation for the average patient where you don't have a reason to believe whether there's aneuploidy one way or the other but you want to confirm that there isn't . . . [such as] a random pregnant mother and it's just a routine case of wanting to determine whether there's Down syndrome." Gauger Decl., Ex. 15 at 261:8-262:3. Thus, there is no cause to add the limitation of an "affirmative" suspicion or presumption.

Second, Sequenom argues that the chromosomes suspected to be aneuploid cannot be the same chromosome as the chromosome presumed to be euploid; these categories are mutually exclusive. The Court agrees, and finds that the plain language of the claim makes clear that, by labeling them the first and second chromosome, the terms are setting up distinct categories. This ties directly to the specification, which explains that the chromosome presumed to be aneuploid is "a control sequence" that is compared against the potentially abnormal sequence. The '017 Patent 6:38-45. Verinata argues that for certain tests, one could analyze the data of chromosomes 18 and 21 against each other; in that instance, the test for aneuploidy of chromosome 21 would have chromosome 21 be suspected to be aneuploid, but the test for aneuploidy of chromosome 18 would have chromosome 21 be presumed to be euploid. However, Sequenom explains that its construction does not preclude this example, because the suspicions and presumptions do not create static categories, but rather they create dynamic categories that are made solely for the purpose of the comparison. Thus, the chromosome cannot be tested against *itself*, but it could in different tests serve as chromosome one or chromosome two. Verinata and its experts agree that this is a limitation of the claim scope. *See* Holmes Decl., Ex. 31 at 123:18-124:15; Verinata & Stanford's Reply Claim Construction Br. at 10-11.

"Wherein said at least one first target chromosome is presumed to be diploid," therefore, is construed as "wherein said first target chromosome, which cannot include the at least one second chromosome suspected to be aneuploid, is presumed to be of normal copy number." "**Wherein said at least one second chromosome is suspected to be aneuploid,"** therefore, is construed as "wherein said second chromosome is suspected to be of abnormal copy number."

"Wherein said at least one first chromosome is presumed to be euploid," therefore, is construed as "wherein said first chromosome, which cannot include the at least one second chromosome suspected to be aneuploid, is presumed to be of normal copy number." **"Wherein said at least one second chromosome is suspected to be aneuploid,"** therefore, is construed as "wherein said second chromosome is suspected to be of abnormal copy number."

G. "Determining the Presence or Absence of a Fetal Aneuploidy"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"determining the presence or absence of a fetal aneuploidy from the results of the statistical analysis of step f)" [Claim 17 of the '017 patent]	No construction necessary	"making an affirmative determination that the fetus does or does not have a fetal aneuploidy from the comparison of the number of copies of the first target chromosome with the number of copies of the second chromosome in step f)"

The parties' argument over the construction of this term is essentially whether the determination of fetal aneuploidy needs to be made "affirmatively." Sequenom argues that its construction clarifies that the claim is limited to a definitive determination, and precludes, for example, a risk score of the likelihood of aneuploidy. Besides that one dispute, they generally agree that the words in the term need not be construed.

The Court finds that neither the patent specification nor the claim supports a limitation that the aneuploidy needs to be determined affirmatively. The specification specifically illustrates an example wherein the tests may yield results that are not statistically significant. *See* The '017 Patent 5:54-6:3. If the result is not statistically significant, then the answer would not be affirmative, and additional

testing may have to be performed. Additionally, the claim calls for "statistical analysis," and therefore calls for a result that will yield a probability, not an affirmative determination. Both the specification and the claim encompass results that may not definitively or affirmatively determine the presence of fetal aneuploidy. Moreover, Sequenom presents no evidence of a clear disavowal of the claim scope.

"Determining the presence or absence of a fetal aneuploidy from the results of the statistical analysis of step f)," therefore, shall be accorded its plain and ordinary meaning because no construction is necessary.

H. "Compare an Amount in Said Mixture"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"compare an amount of at least one first chromosome in said mixture of maternal and fetal genomic DNA to an amount of at least one second chromosome in said mixture" [Claim 1 of the '018 patent]	No construction necessary	"compare an amount of at least one first chromosome to an amount of at least one second chromosome, all chromosomes being within one maternal tissue sample"

The parties disagree about whether the term should include the additional limitation of "all chromosomes being within one maternal tissue sample." Sequenom argues that the repetition of "said mixture" necessarily refers to the *same* said mixture, and the claim should be construed to include this limitation. Verinata disagrees, and argues that no construction is necessary for this term.

Sequenom argues that the claim language supports its proposed construction. Identical terms should be construed to the same meaning in a claim. *See Am. Permahedge, Inc. v. Barcana, Inc.*, 105 F.3d 1441, 1446 (Fed. Cir. 1997). Here, the first "said mixture" is apparently refers to the mixture "of maternal and fetal genomic DNA" that was described in the previous steps. Therefore, Sequenom argues, the second "said mixture" must also refer to the *same* mixture of maternal and fetal genomic DNA that was described in the previous steps.

However, the claim language does not specifically limit performance of the test to a single mixture of maternal and fetal DNA. It could be performed on a different mixtures, or the mixture could

include multiple sets of maternal and fetal DNA. Thus, although "said mixture" is repeated, it does not necessarily follow that the mixture is taken from the same or a single maternal tissue sample. "[T]he use of a definite article ("said" or "the") to refer back to an initial indefinite article does not implicate, let alone mandate the singular." *Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1343 (Fed. Cir. 2008).

Indeed, the specification has examples of tests being conducted on multiple tissue samples. In Table 1, the analysis was performed to yield a comparison of ratios from a set of both normal and Down syndrome samples. The '018 Patent 28:10-25. The specification explains that when the samples are compared against each other, the Down syndrom fetuses have a statistically significant higher ratio number. *Id.* 28:26-42.

Except for the extra limitation that Sequenom argues should be added regarding the same sample, the parties do not dispute the meaning of any other words in the term.

"**Compare an amount of at least one first chromosome in said mixture of maternal and fetal genomic DNA to an amount of at least one second chromosome in said mixture,"** therefore, shall be given its plain and ordinary meaning and shall not be construed.

I. "Solid Phase Amplification and Four-Color Sequencing"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"solid phase amplification of the attached fragments to create attached fragments to create a high density sequencing flow cell" [Claims 3, 4 of the '018 patent]	"amplification (*e.g.*, by polymerase chain reaction) of DNA fragments attached to the surface of a container through or over which reagents can be flowed (*e.g.*, as in the Illumina sequencing platform)"	No construction necessary: Solid phase polymerase-based amplification of the attached fragments to create a high density sequencing flow cell
"Four-color DNA sequencing by synthesis process" [Claims 3, 4 of the '018 patent]	"any DNA sequencing process in which sequencing information is ascertained by detecting incorporation of four differently labeled nucleotides into a DNA strand during synthesis (*e.g.*, as in the Illumina sequencing platform)"	No construction necessary: DNA sequencing by synthesis process using four different dye-labeled dNTPs with photocleavable linkers in which all four dTNPs can be assayed simultaneously

The parties generally agree that these terms can mostly be understood by their ordinary meaning. Sequenom objects to Verinata's deletion of "solid phase" from its proposed construction. Verinata offers no justification for this omission. Sequenom also objects to the inclusion of the example "as in the Illumina sequencing platform" in both constructions, for the reasons stated *supra*.

The Court finds that these terms can be understood by their ordinary meaning. Verinata's definitions do not add any clarity to these terms. A person having ordinary skill in the art would understand these terms by their plain and ordinary meaning.

"Solid phase amplification of the attached fragments to create attached fragments to create a high density sequencing flow cell" and "**four-color DNA sequencing by synthesis process**," therefore, shall be accorded their plain and ordinary meaning because no construction is necessary.

3. The '415 Patent

The '415 patent was also invented by Drs. Quake and Fan, and is owned by Stanford and licensed by Verinata. It is called "Noninvasive Diagnosis of Fetal Aneuploidy by Sequencing," and it was issued on June 5, 2012. Like the '017 and '018 patents, it teaches a method of using massively parallel sequencing and molecular counting of cell-free fetal and maternal DNA in order to determine fetal aneuploidy, without the need to distinguish between fetal and maternal DNA. The '415 Patent, Abstract. The '415 patent's innovation is a technique to correct for sequencing bias. Some regions of a chromosome are copied and sequenced more frequently than others (for example, sequences with a high density of guanine or cytosine). The '415 patent teaches how to count the number of sequence tags mapped to a predefined "window" in each chromosome, which accounts for over- or under-representations of the chromosomes, and also how to use this information to correct for sequencing bias. *Id.*

The relevant portion of the '415 patent claims the following:

> **Claim 1.** A method of testing for an abnormal distribution of a specified chromosome portion in a mixed sample of normally and abnormally distributed chromosome portions obtained from a subject, comprising:
>
> (a) sequencing DNA from **the mixed sample** to obtain sequences from multiple chromosome portions, wherein said sequences comprise a number of sequence tags of

> sufficient length of determined sequence to be assigned to a chromosome location within a genome;
>
> (b) assigning the sequence tags to corresponding chromosome portions including at least the specified chromosome by comparing the determined sequence of the sequence tags to a reference genomic sequence;
>
> (c) determining values for numbers of sequence tags mapping to chromosome portions by using a number of windows of defined length within normally and abnormally distributed chromosome portions to obtain **a first value and a second value** therefrom; and
>
> (d) using the values from step (c) to **determine a differential, between the first value and the second value, which is determinative of whether or not the abnormal distribution exists**.
>
> **Claim 14**. The method of claim 3 further comprising the step of calculating a relationship between numbers of sequence tags and **GC content** associated with sequence tags in a given window and correcting for a higher or lower number of reads resulting from a change in **GC content**.

The '415 Patent 33:53-34:58, 36:18-22 (the construction of the highlighted terms is disputed by the parties). The parties agree on the construction of three terms: (1) "massively parallel sequencing" should be construed as "techniques for sequencing millions of fragments of nucleic acids, *e.g.*, using attachment of randomly fragmented genomic DNA to a planar, optically transparent surface and solid phase amplification to create a high density sequencing flow cell with millions of clusters, each containing ~1,000 copies of template per sq. cm."; (2) "sequence tag" should be construed as "a relatively short (*e.g.*, 15-100) nucleic acid sequence that can be used to identify a certain larger sequence, *e.g.*, be mapped to a chromosome or genomic region or gene"; and (3) "aneuploidy" should be construed as "presence or absence of an entire chromosome, as well as the presence of an entire chromosome, as well as the presence of partial chromosomal duplications or deletions." The parties dispute the construction of four other terms.

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A. "The Mixed Sample"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"the mixed sample" [Claims 1, 3, 10]	"a sample of DNA extracted from the plasma of a pregnant woman, consisting of a mixture of maternal and fetal DNA"	"the mixed sample of normally and abnormally distributed chromosome portions obtained from a subject"

The parties dispute the construction of the term "the mixed sample." Verinata's proposed construction generally defines the sample as a mixture of maternal and fetal DNA, while Sequenom's proposed construction references the definition in the preamble of claim 1.

Verinata's proposed construction is problematic because it is too limited. Verinata's construction defines the mixture as a mixture of maternal and fetal DNA. But claim 1 never discusses the origin of the mixture. It may be from a pregnant mother, but it may also be from another source. Indeed, claim 3 provides, "The method of claim 1 wherein the mixed sample is comprises [*sic*] a mixture of maternal and fetal DNA and wherein the abnormal distribution results from a fetal aneuploidy." Thus, claim 3, which is a dependent claim to claim 1, adds a limitation that is essentially the same construction that Verinata proposes. However, it is a general principle of claim construction that limitations of a dependent claim are not also limitations of the independent claim. *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 910 (Fed. Cir. 2004) (citations omitted) ("As this court has frequently stated, the presence of a dependent claim that adds a particular limitation raises a presumption that the limitation in question is not found in the independent claim."). Therefore, Verinata's proposed construction is incorrect because it creates a limitation in the independent claim that is also created by dependent claim 3.

However, Sequenom's proposed construction is also too limited. The mixed sample cannot mean a mixture of normally and abnormally distributed chromosome portions because that is the very state being tested for. As the preamble explains, it is a method of "*testing for* an abnormal distribution" of chromosomes. Therefore, the tester cannot know beforehand if the mixture contains an abnormal distribution of chromosomes. Furthermore, the sample may contain either a normal *or* an abnormal distribution of chromosomes. Thus, Sequenom's construction, while based in the words of the

preamble, does not properly fit the context of the claim. Instead, the proposed construction would correctly define the term if it clarified that the mixture only had the *possibility* of containing abnormally distributed chromosomes, because this is what is being tested for. At oral arguments, Verinata agreed with this proposed construction.[3]

"The mixed sample," therefore, is construed as "the mixed sample of normally and potentially abnormally distributed chromosome portions obtained from a subject."

B. "A First Value and a Second Value"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"a first value and a second value" [Claim 1]	"a first value and a second value for numbers of sequence tags mapping to chromosome portions"	"a first value and a second value for mapping to different chromosome portions, all chromosome portions being from one sample/subject"

The parties disagree about whether the term "a first value and a second value" should include a limitation that the values from the chromosome portions come from the same sample. Sequenom argues that this limitation is required by the plain meaning of the claims in the patent.

[3] On September 17, 2013, Sequenom filed a letter brief, arguing that the Court's addition of the word "potentially" is improper and constitutes impermissible claim redrafting. Docket No. 132. On September 19, 2013, Verinata filed a response, arguing that Sequenom's letter is unauthorized supplemental claim construction briefing in violation of the Court's local rules. Docket No. 133. The Court agrees with Verinata.

In addition, the Court disagrees that its adopted construction constitutes impermissible claim redrafting. The Federal Circuit has explained that a court may not redraft claim language to render the claim operable or valid where the claim is susceptible to only one reasonable construction in light of the intrinsic record. *Haemonetics Corp. v. Baxter Healthcare Corp.*, 607 F.3d 776, 782 (Fed. Cir. 2010); *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004) (explaining that construing "to" as "at" would constitute impermissible claim redrafting because "nothing in the claims, the specification, or the prosecution history . . . indicates that the patentees here defined 'to' to mean 'at'"). Here, the Court's construction, not Sequenom's construction, is the most reasonable construction in light of the claim language. Independent claim 1 of the '415 patent states that the final step of the method "is determinative of whether or not the abnormal distribution exists." The '415 Patent 34:57-58; *see also id.* at 3:64-4:1, 4:64-67 (specification). Therefore, according to the claim language, it is only after this final method step has been performed that the tester knows if the sample contains abnormally distributed chromosome portions. Accordingly, the Court's construction incorporating the word "potentially" is directly supported by the claim language and is not impermissible claim redrafting.

Verinata argues that the term cannot be limited to coming from the same sample because the patent contains embodiments wherein chromosome portions come from both a single patient and multiple patients. In Example 9, entitled "Comparing Different Patient Samples Using Statistical Analyses (T Statistic)," "multiple patient samples are analyzed in a single process" in which the average t statistic is computed for multiple patient samples, which is then used to determine aneuploidy. The '415 Patent 26:63-27:51. Sequenom's own expert agreed that Example 9 was a test that statistically compared different patient samples in a single process, and this was covered by claim 19. *See* Walter Decl., Ex. 8 at 282:23-285:18. Therefore, the specification supports the construction that does not limit the chromosome portions to being from a single sample.

"A first value and a second value," therefore, is construed as "a first value and a second value for numbers of sequence tags mapping to chromosome portions."

C. "Determine a Differential"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"determine a differential, between the first value and the second value, which is determinative of whether or not the abnormal distribution exists" [Claim 1]	"determine a value showing or relating to a difference between the first and second value, which is used to determine whether or not the abnormal distribution exists"	"determine the difference between the first value and the second value, both values determined from chromosome portions of one sample/subject"

The parties have two disputes regarding the construction of this term. First, similar to the dispute over the last claim term, they disagree about whether the chromosome portions must be from the same sample or subject. Sequenom argues that the term should limited to an analysis of "chromosome portions of one sample/subject," while Verinata argues that the term should not be construed as having that limitation. As discussed *supra*, the Court finds that the specification supports the construction that does not limit the analysis to a single sample or subject.

Second, the parties dispute whether "differential" is limited to an integer difference, or if it can more broadly include a value that only relates to the difference. Sequenom argues that "differential"

should be construed narrowly, as "difference." However, the specification supports a broad definition of differential, including the calculation of a ratio. For example, Figure 1B of the '415 patent shows sequence tag densities in ratio form, and those with a ratio higher than 1 are aneuploid. Sequenom argues that Verinata's proposed construction "just adds vague weasel words," but it offers no particular objection to any particular portion of the proposed construction.

"Determine a differential, between the first value and the second value, which is determinative of whether or not the abnormal distribution exists," therefore, is construed as "determine a value showing or relating to a difference between the first and second value, which is used to determine whether or not the abnormal distribution exists."

D. "GC Content"

Claim Term	Verinata's Proposed Construction	Sequenom's Proposed Construction
"GC content" [Claim 14]	"any measure of the amount of a DNA molecule that is either guanine or cytosine"	No construction necessary Alternatively: "GC content associated with the sequence tags"

The parties do not dispute that "G" refers to "guanine," and "C" refers to "cytosine." However, Verinata proposes a broader construction of "GC content" than Sequenom. Sequenom would limit the GC content measure to sequence tags. It argues that the limitation is required because the term is often used modifying sequence tags. *See, e.g.*, The '415 Patent 17:31-35. However, sometimes the specification uses the term GC content to mean the content of the entire chromosome, not just the sequence tags. *See, e.g.*, The '415 Patent 25:61-63 ("The variations between *chromosomes* with low and high G/C content are eliminated from the data to be examined.").

Sequenom also argues that Verinata's proposed construction is vague, because "any measure" is unclear and not limited. The specification refers to GC content as a range and as a percentage. *See, e.g.*, The '415 Patent 26:14-16, 30-36. There is nothing in the specification that constitutes a clear disavowal of the claim scope that would limit the type of measurement of guanine or cytosine. Thus, the type of measurement should not be limited, and the Court does not find "any measure" to be unclear.

"GC content," therefore, is construed as "any measure of the amount of a DNA molecule that is either guanine or cytosine."

4. The '076 Patent

The '076 patent also stems from the work of the Stanford research team of Drs. Quake and Fan. Entitled "Noninvasive Diagnosis of Fetal Aneuploidy by Sequencing," it was issued on October 23, 2012. It teaches a method to non-invasively detect fetal aneuploidy through direct shotgun or massively parallel sequencing of predefined subsequences of DNA. The '076 Patent, Abstract. Unlike the '017 and '018 patents, the '076 patent teaches a method that utilizes predefined subsequences of DNA, instead of random sequencing. *Id.* at claim 1. Verinata is the licensee of the '076 patent, and Verinata and Stanford allege that Ariosa is infringing the patent with its Harmony Prenatal Test.

The relevant portion of the '076 patent claims the following:

> **Claim 1.** A method of testing for an abnormal distribution of a chromosome in a sample comprising a mixture of **maternal** and fetal DNA, comprising the steps of:
>
> (a) obtaining maternal and fetal DNA from said sample;
>
> (b) **sequencing predefined subsequences of the maternal and fetal DNA** to obtain a plurality of sequence tags aligning to the predefined subsequences, wherein said sequence tags are of sufficient length to be assigned to a specific predefined subsequence, wherein the predefined subsequences are from a plurality of different chromosomes, and wherein said plurality of different chromosomes comprise at least one **first chromosome suspected of having an abnormal distribution** in said sample and at least one **second chromosome presumed to be normally distributed** in said sample;
>
> (c) assigning the plurality of sequence tags to their corresponding predetermined subsequences;
>
> (d) determining a number of sequence tags aligning to the predetermined subsequences of said first chromosome and a number of sequence tags to the predetermined subsequences of the second chromosome; and
>
> (e) comparing the numbers from step (d) to determine the presence or absence of an abnormal distribution of said first chromosome.

The '076 Patent 35:9-33 (the construction of the highlighted terms is disputed by the parties). The parties agree that the term "sequence tags" should be construed as "relatively short nucleic acid sequences that can be used to identify certain larger sequences." They disagree on the construction of several other terms within claim 1.

A. "Sequencing Predefined Subsequences"

Claim Term	Verinata's Proposed Construction	Ariosa's Proposed Construction
"sequencing predefined subsequences"	See below	"determining the order of nucleotides to selectively capture sample molecules containing sequences selected *a priori*"
"sequencing predefined subsequences of the maternal and fetal DNA"	"sequencing predetermined polymorphism independent subsequences of pregnant human female and fetal chromosomes"	See above
"maternal"	"pregnant human female"	"of the mother"

The parties dispute whether the claim is "polymorphism independent" (*i.e.*, does not depend on differences between maternal and fetal DNA sequences), and whether the claim should be limited to the selective capture of sample molecules.

First, Verinata argues that the claim teaches the sequencing of "polymorphism independent subsequences," as demonstrated by numerous statements throughout the patent that the sequencing is independent of the differences between maternal and fetal DNA. For example, the specification explains that, while other non-invasive tests for fetal aneuploidy depend on distinguishing between the maternal and fetal DNA, the research of Drs. Quake and Fan shows it is "possible in principle to use digital PCR to create a universal, polymorphism independent test for fetal aneuploidy." The '076 Patent 2:4-17; *see also id.* at 20:36-39 ("[t]he sequencing approach is polymorphism-independent"); *id.* at Abstract ("This method does not require the differentiation of fetal versus maternal DNA."); *id.* at 4:23-25 ("This forms the basis of a universal, polymorphism-independent non-invasive diagnostic test for fetal aneuploidy.").

Ariosa attempts to distinguish these passages by arguing that the patent discloses two types of sequencing methods, random and targeted, and the only polymorphism independent sequencing methods discussed in the specification are the random or "shotgun" sequencing methods, not the targeted sequencing method described by claim 1. However, many of the passages that describe the invention as polymorphism independent do not specify the type of sequencing that is being used. The patent's

abstract and its description distinguishing prior art are not limited to only targeted sequencing. Ariosa does not point to any other aspect of the specification or the claims that would limit this term. There is no clear disavowal of claim scope that would limit the term to require the sequences to depend on the differences between maternal and fetal DNA sequences. Therefore, the claim should be construed as "polymorphism independent."

Second, Ariosa's proposed construction defines "sequencing" as "selectively capturing sample molecules." Ariosa explains that DNA is a molecule and DNA sequencing can only be performed upon DNA molecules. It argues that a lay juror would need the terms "sequencing" and "subsequences" defined for them, and Verinata's construction should be rejected because it declines to construe these terms. Ariosa argues that its definition is aligned with the specification: "This alternative method selectively ignores certain sequence information by using a sequencing method which *selectively captures sample molecules* containing certain predefined subsequences." The '076 Patent 14:25-28 (emphasis added); *see also id.* at 13:54-14:1 ("One may use sequencing methods which select a priori sequences which map to the chromosomes of interest . . . In sequencing selected subsequences, one may employ sequence-based methodologies such as sequencing by array, or capture beads with specific genomic sequences used as capture probes.").

However, claim 1 is broader than the portion of the specification that describes the method of selectively capturing sample molecules. The specification expressly does not limit the patent to that method of sequencing, by stating that it is "[a]nother method" or a method that "one may employ." *Id.* at 13:53, 65. Indeed, the patent explains that "[t]he sequencing method is *in one aspect* contrary to conventional massively parallel sequencing methodologies," an "alternative method." *Id.* at 14:22-25 (emphasis added). Claim 3, which is dependent to claim 1, teaches a method "wherein the sequencing comprises massively parallel sequencing of the predefined subsequences." *Id.* at 35:39-41. Thus, claim 1 must encompass sequencing types that would include both massively parallel sequencing and other types of sequencing. However, as the specification states, the subsequencing method of selectively capturing sample molecules is an "alternative method" that is "contrary to conventional massively parallel sequencing methodologies." Moreover, the specification lists examples of how to selectively sequence the subsequences of interest, such as array or capture beads, but it also explains that

"[e]mulsion PCR, as used in the 454 system, the SOLiD system, and Polonator (Dover Systems) and *others may also be used*." *Id.* at 14:12-15 (emphasis added). Thus, although the specification lists several examples of how to sequence the predefined subsequences, including the selective capture of molecules, this is not an exhaustive or limiting list. Therefore, this is only one of several preferred embodiments, and it cannot be a limitation of claim 1. Accordingly, there is no clear disavowal of claim scope limiting sequencing to "selectively capture sample molecules."

Additionally, the Court does not find that "sequencing" or "subsequences" would not be understood by a lay juror or a person having ordinary skill in the art. Moreover, Ariosa's proposed construction incorporating dictionary definitions without support from the intrinsic evidence is disfavored. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1320 (Fed. Cir. 2005).

Finally, the parties dispute how the term "maternal" should be construed. The Court finds that the ordinary meaning of "maternal" is readily apparent even to lay persons, and therefore need not be construed.

"Sequencing predefined subsequences of the maternal and fetal DNA," therefore is construed as "sequencing predetermined polymorphism-independent subsequences of maternal and fetal chromosomes."

B. "First Chromosome Suspected"; "Second Chromosome Presumed"

Claim Term	Verinata's Proposed Construction	Ariosa's Proposed Construction
"first chromosome suspected of having an abnormal distribution"	No construction necessary	"first chromosome hypothesized prior to running the test to have an abnormal distribution"
"second chromosome presumed to be normally distributed"	No construction necessary	"second chromosome different from the first chromosome that is assumed with confidence prior to performing the test to have a normal distribution"

The parties' dispute in the construction of these terms is threefold: (1) Ariosa's proposed definitions of "suspected" and "presumed," (2) whether the second chromosome must be different from

the first chromosome, and (3) whether the suspicion or presumption must occur prior to performing the test.

First, Ariosa defines "suspected" as "hypothesized," and "presumed" as "assumed with confidence." The source of these definitions is from extrinsic evidence, dictionaries. Ariosa offers no intrinsic evidence of the definitions of these words. The Court finds that these terms have a plain and ordinary meaning that would be readily understood by lay jurors. Moreover, these dictionary definitions may have a different connotation that is not captured by the original terms. Because they are not tied to the claims or specification, it is impossible to know what alternative dictionary definition most accurately conveys the meaning and connotation of the words. *See Phillips*, 415 F.3d at 1320.

Second, Verinata argues that the specification allows for the first chromosome to also be the second chromosome, while Sequenom argues that they must be different. The specification suggests in one embodiment that certain chromosomes are preferred reference chromosomes: "chromosomes 18, 8, 2, 7, 12, 21 (except in suspected Down syndrome), 14, 9, and 11 may be used as the nominal diploid chromosome if looking for trisomy." The '076 Patent 5:59-62. Verinata argues that this proves that certain chromosomes can serve as the "second" reference chromosome, even if they are know to potentially exhibit aneuploidy (*e.g.*, chromosome 21 could be a reference chromosome to test for trisomy 18, even though it is a chromosome that often exhibits aneuploidy, causing Down syndrome). Ariosa argues that the parenthetical proves that the chromosome suspected of being aneuploid cannot also be the same chromosome to serve as a reference chromosome. Additionally, both parties point to the "t-statistic" experiment, in which multiple chromosomes are compared against each other, as supporting their arguments. *See* The '076 Patent 27:10-67. Interpreting the specification, it seems that both parties are partially correct. Verinata is correct that a chromosome that sometimes may be suspected of aneuploidy can also serve as a reference chromosome. However, the specification also makes clear that a chromosome could not be tested against itself (chromosome 21 could not be used as a reference to test for Down syndrome). In that sense, Ariosa's construction is accurate – the second chromosome must be different from the first chromosome. Moreover, the plain language of the claim, by specifically naming a first and second chromosome, requires an interpretation that the first and

second chromosomes are different. But Ariosa's construction does not preclude the second chromosome from also serving as a first chromosome to test for a different aneuploidy.

Third, Ariosa argues that the determination of which chromosomes are suspected to be aneuploid, and which will serve as a reference chromosome, must be made prior to running the test. Verinata argues that this interpretation would preclude the t-statistic example in the specification, where multiple chromosomes were tested against each other, and several could have served as either the suspect chromosome or the reference chromosome. The Court agrees. The claim cannot be construed to include a limitation that would bar the example from the specification.

"First chromosome suspected of having an abnormal distribution," therefore, requires no construction. "**Second chromosome presumed to be normally distributed"** is construed as "second chromosome, different from the first chromosome, presumed to be normally distributed."

5. The '430 Patent

Finally, the '430 patent, entitled "Methods of Fetal Abnormality Detection," was invented by a team of Verinata researchers and issued on November 27, 2012. The patent teaches methods for "selectively enriching non-random polynucleotide sequences[,] . . . generating libraries of sequences[, and] . . . using selectively enriched non-random polynucleotide sequences for detection of fetal aneuploidy." The '430 Patent, Abstract. In the claims at issue, the method for detecting fetal aneuploidy utilizes blood samples from multiple pregnant women, which are then pooled and sequenced together.

The relevant portion of the '430 patent claims the following:

> **Claim 1.** A method for determining a presence or absence of a fetal aneuploidy in a fetus for each of a plurality of maternal blood samples obtained from a plurality of different pregnant women, said maternal blood samples comprising fetal and maternal cell-free genomic DNA, said method comprising:
>
> (a) obtaining a fetal and maternal cell-free genomic DNA sample from each of the plurality of maternal blood samples;
>
> (b) **selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample** of (a) to **generate a library derived from** each fetal and maternal cell-free genomic DNA sample of enriched and indexed fetal and maternal non-random polynucleotide sequences, wherein each library of enriched and indexed fetal and maternal non-random polynucleotide sequences

includes an indexing nucleotide sequence which identifies a maternal blood sample of the plurality of maternal blood samples, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from a first chromosome tested for being aneuploid and at least 100 different non-random polynucleotide sequences selected from a **reference chromosome**, wherein the first chromosome tested for being aneuploid and the **reference chromosome** are different, and wherein each of said plurality of non-random polynucleotide sequences is from 10 to 1000 nucleotide bases in length,

(c) pooling the libraries generated in (b) to produce a pool of enriched and indexed fetal and maternal non-random polynucleotide sequences;

(d) performing massively parallel sequencing of the pool of enriched and indexed fetal and maternal non-random polynucleotide sequences of (c) to produce **sequence reads corresponding to** enriched and indexed fetal and maternal non-random polynucleotide sequences of each of the at least 100 different non-random polynucleotide sequences selected from the first chromosome tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences of each of the at least 100 different non-random polynucleotide sequences selected from the **reference chromosome**;

(e) based on the indexing nucleotide sequence, for each of the plurality of maternal blood samples, enumerating sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the first chromosome tested for being aneuploid and sequence reads corresponding to enriched and indexed fetal and maternal non-random polynucleotide sequences selected from the **reference chromosome**; and

f) for each of the plurality of maternal blood samples, determining the presence or absence of a fetal aneuploidy comprising using a number of enumerated sequence reads corresponding to the first chromosome and a number of enumerated sequence reads corresponding to the **reference chromosome** of (e).

Claim 19. A method for determining a presence or absence of a fetal aneuploidy in a fetus for each of a plurality of maternal blood samples obtained from a plurality of different pregnant women, said maternal blood samples comprising fetal and maternal cell-free genomic DNA, said method comprising: . . .

(b) selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample of (a) to generate a library derived from each fetal and maternal cell-free genomic DNA sample of enriched and indexed fetal and maternal non-random polynucleotide sequences, wherein each library of enriched and indexed fetal and maternal non-random polynucleotide sequences includes an indexing nucleotide sequence which identifies a maternal blood sample of the plurality of maternal blood samples, wherein said plurality of non-random polynucleotide sequences comprises at least 100 different non-random polynucleotide sequences selected from at least one chromosome region tested for being aneuploid and at least 100 different non-random polynucleotide sequences selected from at least one **chromosome control region**, wherein the at least one chromosome region tested for being aneuploid and the at least one **chromosome control region** are different, and wherein each of said plurality of non-random polynucleotide sequences is from 10 to 1000 nucleotide bases in length; . . .

The '430 Patent 63:9-67; 65:12-40 (the construction of the highlighted terms is disputed by the parties). The parties agree that "fetal and maternal cell-free genomic DNA" should be construed as "DNA of the mother and the fetus that has been released from cells into the maternal bloodstream." They dispute the construction of several other terms.

A. "Selectively Enriching a Plurality of Fetal and Maternal DNA"

Claim Term	**Verinata's Proposed Construction**	**Ariosa's Proposed Construction**
"selectively enriching" [Claims 1, 19]	See below	"increasing the concentration of a selected subset relative to the remainder of the set"
"non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample" [Claims 1, 19]	See below	"specific molecules selected from each sample of cell-free DNA of the mother and fetus"
"selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample" [Claims 1, 19]	"enriching a plurality of non-random nucleic acid sequences of each fetal and maternal cell-free genomic DNA sample that meet sequence and/or location criteria selected to facilitate aneuploidy detection"	See above

The parties disagree about whether or how this term should be broken up, and over the construction of each portion.

First, Ariosa proposes construing "sequences" as "specific molecules." Ariosa contends that DNA is made up of molecules, and this construction would aid the lay juror in understanding the term. However, Verinata argues that this is an inaccurate and inappropriate construction. Not a single claim in the '430 patent uses the word "molecule," and the specification never refers to the selective enrichment of "molecules" or "specific molecules." Furthermore, Verinata argues that substituting "molecules" for "sequences" would add a limitation not provided for in the claim, because certain specific enrichment procedures called for in the embodiments could not reasonably be performed on molecules. For example, PCR-based enrichment methods use primers that flank a specific DNA sequence of interest, but would not work on an entire molecule of DNA. Other enrichment methods

may work on the complement to the sequence of interest, instead of the actual molecules. The specification repeatedly refers to the selective enrichment of sequences, not molecules. There is nothing in the specification or the claims that constitutes a clear disavowal of the claim scope that would limit "sequences" to mean only "specific molecules." Moreover, although it is not disputed that DNA is made of molecules, "molecules" is a very broad term, and the components of DNA are a very specific type of molecule, as even a lay juror would understand. Thus, Ariosa's proposed construction is unhelpful and not supported by the claim or specification. Verinata's proposed construction of this term replaces polynucleotide with nucleic acid. This definition may be more accessible to lay jurors, and Ariosa does not have a particular objection to this definition.

Second, Ariosa proposes construing "selectively enriching" as "increasing the concentration of a selected subset relative to the remainder of the set." In support of this construction, Ariosa cites the specification, which it argues equates enriching with amplifying. *See, e.g.*, The '430 Patent 9:10-14 (explaining how "polynucleotide sequences using this technique can be enriched (e.g., amplified) in practice"). However, stating that amplification is an *example* of enrichment is not equivalent to stating that amplification is identical to enrichment. Nowhere in the specification or the claim is there a clear disavowal of the scope of enrichment that would limit it to amplification. Indeed, by citing amplification as an example of enrichment, the plain meaning of the specification is that enrichment includes, but is not limited to, amplification. Thus, Ariosa's proposed construction is contradicted by the specification.

Verinata's proposal does not construe the term "enriching," but it defines "selectively" as "criteria selected to facilitate aneuploidy detection." Support for Verinata's proposed construction is found in the preamble of the claim, which describes the purpose of the method as "determining a presence or absence of a fetal aneuploidy." Verinata argues that the purpose of the selective enrichment must serve the purpose of the entire claim, and therefore this limitation is appropriate. Ariosa argues that this addition changes the scope of the claim. However, this limitation is already incorporated into the preamble of the claim, and therefore does not change the scope.

"Selectively enriching a plurality of non-random polynucleotide sequences of each fetal and maternal cell-free genomic DNA sample," therefore, is construed as "enriching a plurality of non-

random nucleic acid sequences of each fetal and maternal cell-free genomic DNA sample that meet sequence and/or location criteria selected to facilitate aneuploidy detection."

B. "Generate a Library"

Claim Term	Verinata's Proposed Construction	Ariosa's Proposed Construction
"generate a library derived from" [Claims 1, 19]	"library" means "a set of nucleic acid sequences" No further construction necessary.	"produce a collection through multi-step amplification that originates from"

The parties dispute whether generating a library is limited to "multi-step amplification," or whether a library can be generated by either a single or a multi-step amplification process. They also dispute whether "derived from" means "that originates from."

Ariosa argues that the term should be limited to "multi-step amplification" because the patentee, acting as her own lexicographer, wrote an express definition. In a section entitled "Library Formation," the patent explains:

> In another aspect, a method is provided for generating a library of selectively enriched non-random polynucleotide sequences comprising a) amplifying one or more polynucleotide sequences with a first set of oligonucleotide pairs, b) amplifying the product of a) with a second set of oligonucleotides pairs; and c) amplifying the product of b) with a third set of oligonucleotide pairs.

The '430 Patent 13:65-14:5. This three-step amplification process is described three more times in this section. *Id.* at 14:21-55.

To act as its own lexicographer, the patentee must clearly set out her own definition with "reasonable clarity, deliberateness, and precision," in a manner "so as to give one of ordinary skill in the art notice of the change." *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994). Here, there is no clear statement that would notify a person of ordinary skill in the art that the inventor is defining library in this specific manner. The specification describes this multi-step amplification process by explaining that it is "another aspect," which would more likely be understood as merely referring to a preferred embodiment, not a novel definition. Indeed, in another passage, the patent defines the library as either a single or multi-step amplification process: "In another aspect, the provided invention includes

methods for generating a library of enriched polynucleotide sequences. A library can be generated by the use of *one or more* amplification steps . . . ." *Id.* at 6:8-11 (emphasis added). Thus, there is no clear disavowal of claim scope or clear notification that the patentee is acting as her own lexicographer.

Ariosa also argues that its proposed construction of "multi-step amplification" is required to preserve validity, because the patent is not enabled for the creation of a library using only one amplification step. Although the patent lays out the specific steps needed to create a library through a multi-step amplification process, the patent does not explain how to create a library through a single amplification process. Ariosa argues that, in the state of the art at the time of the invention, a person having ordinary skill in the art would not have known how to create a library through a single amplification process. However, Ariosa offers no support for this assertion. "[C]laims can only be construed to preserve their validity where the proposed claim construction is 'practicable,' is based on sound claim construction principles, and does not revise or ignore the explicit language of the claims." *Generation II Orthotics Inc. v. Med. Tech. Inc.*, 263 F.3d 1356, 1365 (Fed. Cir. 2001). Here, the proposed construction would add a limitation that is not supported by the specification or claim, which is not permitted when construing a term to preserve validity. Furthermore, there is no evidence that Ariosa's proposed construction of library as a multi-step amplification process is necessary to preserve validity. Thus, the proposal must be rejected.

Second, Ariosa's proposed construction defines the term "derived" as "originates from." The proposed construction is from a dictionary definition, not intrinsic evidence. Ariosa argues that the claim language of the patent requires this limitation because it expressly differentiates between the origin of the sequences of the library (*i.e.*, where they are derived from) and the manipulations carried out on the sequences in the library. However, a broader understanding of the term could also be supported by the claim language. The library need not consist solely of DNA fragments taken directly from the sample, but may also consist of manipulated or amplified sequences related to the original sample but transformed in certain ways. Ariosa provides no support for why the term would exclude this type of library, or why the dictionary definition is preferable to the claim language, which would readily be understood by lay jurors.

"Generate a library derived from," therefore, is construed as "generate a set of nucleic acid sequences derived from."

C. "Reference Chromosome" and "Chromosome Control Region"

Claim Term	Verinata's Proposed Construction	Ariosa's Proposed Construction
"reference chromosome" [Claim 1]	"chromosome other than the particular chromosome that is being tested for aneuploidy, information from which is used in the evaluation of aneuploidy for the particular chromosome that is being tested"	"chromosome that is not being tested for aneuploidy"
"chromosome control region" [Claim 19]	"chromosome region other than the particular chromosome region that is being tested for aneuploidy, information from which is used in the evaluation of aneuploidy for the particular chromosome region that is being tested"	"segment from a chromosome not being tested for aneuploidy"

The general dispute over the construction of these terms is whether the reference chromosome or the chromosome control region is limited to chromosomes that are not also tested for aneuploidy. Ariosa argues that a reference chromosome cannot also be tested for aneuploidy. Verinata argues that, although the reference chromosome must be different that the chromosome suspected of aneuploidy, it can also be tested for aneuploidy.

The Court disagrees with Ariosa's proposed limitation, which would preclude reference chromosomes from also being tested for aneuploidy. The claim language only provides that the reference or control chromosomes are different from those being tested. Chromosomes such as chromosome 13, 18, and 21 are often tested for aneuploidy, but can also serve as reference chromosomes. This is possible because it is highly unlikely that a fetus could be aneuploid in multiple chromosomes. Therefore, chromosome 18 can serve as a reference chromosome for chromosome 21,

and vice versa. Ariosa's construction would create a limitation that is not supported by the specification or the claims. The claim merely limits the reference chromosome to being "different" from the chromosome being tested for aneuploidy: "a reference chromosome, wherein the first chromosome tested for aneuploid and the reference chromosome are different." The '430 Patent 63:33-35. Ariosa offers no support for its argument that there is a clear disavowal of claim scope that would limit the reference chromosome so that it could not also be tested for aneuploidy.

Furthermore, Ariosa's arguments regarding the prosecution history are also unpersuasive. The parties agree that the prosecution history requires that the reference and control be "different" from the tested chromosome. However, the prosecution history does not also limit the testing of the reference chromosomes for aneuploidy.

"**Reference chromosome,"** therefore, is construed as "a chromosome different from the particular chromosome that is being tested for aneuploidy."[4] **"Chromosome control region"** is construed as "a chromosome region different from the particular chromosome region that is being tested for aneuploidy."

D. "Sequence Reads Corresponding To"

Claim Term	Verinata's Proposed Construction	Ariosa's Proposed Construction
"sequence reads corresponding to" [Claims 1, 19]	No construction necessary	"ordered nucleotide arrangements from"

Finally, Verinata argues that the term "sequence reads corresponding to" need not be construed, while Ariosa proposes that the term be construed as "ordered nucleotide arrangements from." Ariosa argues that "sequence reads" will confuse a lay juror, who will not understand that this refers to a DNA sequence. However, the Court does not find that a lay juror will not understand that a "sequence" refers to a DNA sequence, given the context of the entire patent. It has a plain and ordinary meaning. In any

[4] This is an alternative construction that Verinata has proposed, which is simpler and more closely tracks the language in claim 1.

event, the Court does not find that "ordered nucleotide arrangement" adds any greater clarity to the term; it may only add more confusion to a term which would be understood by the lay jury.

"Sequence reads corresponding to," therefore, shall be accorded its plain and ordinary meaning because no construction is necessary.

CONCLUSION

For the foregoing reasons and for good cause shown, the Court adopts the constructions set forth above.

IT IS SO ORDERED.

Dated: October 16, 2013

SUSAN ILLSTON
United States District Judge